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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**RE: [Docket No. 99D-1541 – Draft guidance for Industry on Establishing
Pregnancy Registries (64 Federal Register 30041 (June 4, 1999))]**

Merck & Co., Inc. is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than \$2 Billion, annually, on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market, today. Research, by its nature, is a multidisciplinary and highly risk-intensive business. It depends upon many variables, including: prolific source materials, first class talent, adequate funding, efficient and effective quality processes and procedures, and a predictable regulatory environment.

Merck's research scientists ensure that our Research process continues to identify medically important product candidates from thousands of chemical and molecular entities screened, each year. Only one in ten of these research product candidates is selected to enter the Development testing programs. The medicines which Merck ultimately presents to worldwide health authorities for marketing approval are those that have met the highest technical standards available and those that are able to withstand the most critical regulatory review.

Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. Regulators must be reasonable, unbiased and efficient when they review the quality, effectiveness and safety of our products. It is in both of our interests to see that important therapeutic advances reach patients without unnecessary or unusual delays.

Merck has been operating a Pregnancy Registry Program since 1995. Products for which registries currently exist include VARIVAX®, SINGULAIR®, MAXALT®, and

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VIOXX® and Merck participates in the antiretroviral pregnancy registry currently run by PharmaResearch Corporation. Merck also participated in the rubella vaccine-related registry maintained by CDC in the past. With this experience in the field, we feel qualified to add our comments to those received from other sources regarding FDA's draft guidance document on the establishment and operation of pregnancy registries.

Merck wishes to commend FDA on its efforts to provide thoughtful and comprehensive guidance for industry in this area. It is evident by the scope and detail of the issues covered in the document that much background work was done to create this draft guidance. We wish to add the following commentary:

1. Merck does not endorse the opinion submitted by other parties that registries should be established exclusively for drugs with suspected risks to pregnancy outcomes, based on animal studies or previous clinical data. Adoption of this premise would preclude registries that may provide reassurance to health care providers and consumers. Instead, we would suggest that FDA use the statement that, "the Sponsor may develop a pregnancy registry for a new product with no known safety concerns at product approval. In these cases, the Sponsor may choose to develop a pregnancy registry for products likely to be used in women of childbearing potential in order to inform and guide health care providers."
2. The statement that "spontaneous reports are inherently retrospective" may be true of Adverse Event reports but is not, in our experience, true of exposure in pregnancy reports. In Merck's experience, most reports come from consumers/providers requesting information on exposure in pregnancy before the outcome of the pregnancy is known (a prospective report). In some cases, this information is requested to help make a pregnancy termination decision. In the pregnancy registry for VARIVAX®, for example, the ratio of prospective reports to retrospective reports was 408 to 19.
3. Merck treats reports of exposure in pregnancy as spontaneous reports and does not request a causality assessment. Adverse outcomes are reported to FDA on an individual basis (15 day alert reports) and as cumulative updates in the Periodic Safety Update Reports (PSURs). All reports are clearly marked as being enrolled in a pregnancy registry so that FDA is aware that the *outcome* information was solicited.
4. The draft Guidance states that pregnancy registry information may "quantify long-term effects such as delayed development, other neurological impairments, or any effects that might be detected in older children previously exposed in utero". This is very difficult information to collect, analyze, and quantify due to the many confounding factors which occur in early childhood. This would also require very burdensome and long-term follow-up. The effort to obtain such information may not be justified by the amount and quality of the information derived.

5. The draft Guidance suggests that collecting data from health care providers (HCPs) and getting informed consent are mutually exclusive. We currently obtain consent through the HCP and thereby get permission to obtain outcome information and to obtain medical records from both prenatal and pediatric providers to confirm outcomes.

6. The document suggests that the protocol and informed consent document be cleared by an IRB. Merck views the registries as intensive postmarketing surveillance procedures, not as studies, therefore we do not request or require IRB clearance.


7. We have concerns with asking specific questions about maternal behavior such as smoking, alcohol use and illicit drug use which may be misconstrued by the reporters as an attempt by the sponsor to rest blame elsewhere and so have avoided asking these specific questions. We use the phrase, "Describe any other relevant information (concurrent medical conditions, exposure to x-rays, teratogens, alcohol, etc.)" on our questionnaires to try to obtain this information.

8. Merck does not agree with the suggestion in the draft Guidance to establish a comparison group. We do not believe we have the right to collect information on anyone who has not been exposed to our product or who does not come to us voluntarily with pregnancy information.

In conclusion, we wish to commend FDA on its efforts to promote the establishment of pregnancy registries to ensure the safe treatment of disease in this special population. Based on our extensive experience with such registries, Merck offers, herein, our suggestions to refine the draft guidance.

We welcome the opportunity to comment on this Guidance and, if appropriate, to meet with you to discuss these issues.

Sincerely,



Bonnie J. Goldmann, MD

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